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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/807,519	09/17/2001	Mitchell Keegan	50179-088	9129

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EXAMINER	
MARVICH, MARIA	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 05/05/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/807,519	KEEGAN ET AL.	
	Examiner	Art Unit	
	Maria B Marvich, PhD	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 February 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,6 and 8-13* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,6 and 8-13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *02 December 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10/23/03; 2/13/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This office action is in response to an amendment filed 2/13/04. Claims 4, 5, 7 and 14-28 have been cancelled. Claim 1 has been amended. Claims 1-3, 6 and 8-13 are pending and under consideration.

Response to Amendment

Any rejection of record in the previous action not addressed in this office action is withdrawn. The new grounds of rejection herein were necessitated by amendment and, therefore, this action is **Final**.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3, 6 and 8-13 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new rejection necessitated by applicant's amendment. This is a New Matter rejection**.

The limitation that the heterologous sequence is "mature" somatotropin has been added to claim 1. Applicant has not indicated where support for this limitation is found. The examiner

has been unable to find literal support in the originally filed specification for the limitation of "mature somatotropin". Therefore, the limitation is impermissible NEW MATTER.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 8-11 and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ballance (US 2003/0104578; see entire document) in view of Paulson et al (US 5,858,751; see entire document) further in view of Eskridge et al (Journal of Cellular Biology, December 1986,Vol 103(6) pp 2263-2272; see entire document). **This is a new rejection necessitated by applicant's amendment.**

Applicants claim an expression cassette comprised of an insulin secretory signal linked to a heterologous sequence encoding mature somatotropin and a method of producing somatotropin.

Ballance et al teach the construction of growth hormone (GH) fusion proteins (see e.g. abstract). Somatotropin is also known as Growth Hormone. GH was cleaved of the leader sequence and the first 8 base pairs. A yeast promoter, signal sequence and the first 8 bp of the GH were attached to the 5' end (see e.g. page 5, paragraph 0071). And this mature growth hormone was cloned downstream of an HSA/Mfα-1 fusion leader sequence for enhanced secretion in yeast (see e.g. page 5, paragraph 0073).

Ballance does not teach use of the insulin secretory signal fused to mature somatotropin.

Paulson et al teach fusion of their gene of interest (i.e. α-2, 3-N Sialytransferase) to a pre-insulin secretory signal in order to generate a soluble, secreted form of their gene product of interest (see e.g. column 31, line 35- column 32, line 22 and column 46, line 1-22).

Eskridge et al determined that the first 38 amino acids of the preproinsulin (ppI) sequence encoded all the information necessary to mediate the efficient translocation of a fused protein, chloramphenical acetyltransferase (page 2265 second paragraph). Therefore, Eskridge et al. demonstrated that the ppI signal sequence encodes all the information necessary to translocate and secrete heterologous proteins (abstract).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the HSA/Mfα-1 fusion leader sequence taught by Ballance with the insulin secretory signal of Paulson et al in which sequences are identified by Eskridge et al because Ballance teach that it is within the ordinary skill of the art to express mature somatotropin using a heterologous signal sequence and because Paulson et al further in view of Eskridge et al teach that it is within the ordinary skill of the art to use an insulin secretory signal to secrete a heterologous protein. One would have been motivated to do so in order to receive the expected benefit of an isolatable soluble secreted Growth Hormone (Paulson et al. column 31, line 50-52 and Eskridge et al. page 2265, second paragraph) beneficial for treatment of a variety of disease such as dwarfism (see Ballance page 1, paragraph 0004). Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Response to Arguments

Applicants traverse the rejection of claims 1, 8-11 and 13 under 35 U.S.C. 103(a) on pages 5-7 of the amendment filed 2/13/04. Applicants argue that the combined art fails to teach or suggest replacement of a homogenous secretory signal with a heterogenous secretory signal i.e. the insulin secretory signal to obtain enhanced secretion of a recombinant protein. The primary reference, it is argued, teaches a heterologous secretory signal that is not the insulin secretory signal linked to a precursor, not mature, protein and does not teach that secretion can be achieved in any cells other than yeast cells. Neither Paulson et al nor Eskridge et al cure these deficiencies in the primary reference. Moreover, Paulson et al and Eskridge et al do not teach that the heterologous protein fused to the insulin secretory signal is somatotropin. The references do not teach enhanced secretion of the heterologous protein or that the insulin secretory sequence replaces the endogenous signal sequence of the heterologous protein. Applicants also state that Eskridge et al teach away from the use of the insulin secretory signal alone as it teaches use of additional sequences with the insulin secretory signal sequence. This is indicated by the fact that while applicants were aware of the region of the amino terminus that constitutes the secretion signal, it is not selected as the secretory sequence alone.

Applicants' arguments filed 2/13/04 have been considered but are not persuasive. As amended, the claims have added the limitation that somatotropin be mature. However, as previously recited, the claims contained no implied or implicit or explicit requirement that either the secretory signal sequence of the somatotropin sequence be replaced by the insulin secretory sequence or that the protein be secreted in cells other than yeast. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the

claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). During prosecution, claims must be interpreted as broadly as their terms reasonably allow. Applicants would like to rely on descriptions of the invention that are not reasonably applied to the claims as written.

Ballance teaches construction of a fusion protein comprising mature somatotropin fused to a secretory signal for production of the mature protein. Ballance teaches deletion of the natural signal sequence and attachment to a heterologous signal sequence. Furthermore, Ballance teaches that the fusion protein can be secreted from a variety of cells such as mammalian (see e.g. page 2, paragraph 0012). Paulson et al and Eskridge et al as secondary references teach that the secretory sequence from insulin can be used for the production and secretion of heterologous proteins. As secondary references, it not necessary that these references also teach that the heterologous protein is somatotropin only that the combination with the primary reference would have made the instant invention obvious. Eskridge et al does not teach away from use of the insulin secretory sequence but rather teaches that it is well known in the art to identify sequences of the insulin prepro sequence required for secretion and attach these sequences to a heterologous protein coding sequences for translocation and secretion of the heterologous protein. That Eskridge et al teach additional sequences does not teach away from use of the insulin secretory sequence as the instantly rejected claims include no limitation to specific sequences of the insulin secretory sequence nor exclusion of additional sequences. Given the teachings of Paulson et al further in view of Eskridge et al, it would have been obvious to isolate and use the insulin secretory signal sequence to translocate and secrete heterologous proteins.

Conclusion

No Claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria B Marvich, PhD whose telephone number is (571)-272-0774. The examiner can normally be reached on M-F (6:30-3:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, PhD can be reached on (571)-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Maria B Marvich, PhD
Examiner
Art Unit 1636

April 21, 2004

GERRY LEFFERS
PRIMARY EXAMINER